Original article

Semen donors and STD screening

J M Craig, C L R Barratt, G R Kinghorn

Aim: The British Andrology Society recommends screening semen donors for sexually transmitted infections to minimise the risk of pathogen transmission to the mother and fetus. The aim was to review recent findings of semen donor screening and, if appropriate, recommend changes to the screening protocol.
Subjects: 175 consecutive men attending for STD screening between January 1992 and December 1995 who had been preselected by the Department of Obstetrics and Gynaecology as suitable semen donors.
Methods: Retrospective review of case notes and group comparison of demographic and sexual history data.
Results: 11 men (6%) had evidence of infection, excluding CMV seropositivity, at their first STD screen. After semen donation, 109 men (63%) were rescreened and, of these, 12% had positive findings. Positive findings at initial screening were predicted by a history of more than one partner in the preceding 6 months (OR 7·11, 95% CI 1·66–30·4) but it did not predict rescreening findings. Other factors such as age, marital status, employment status or past STDs were not predictive for either screen.
Discussion: Less than 20% of initial volunteers meet the full criteria of high quality post-thaw semen, no transmissible genetic disorders, and no transmissible pathogens. Sexual history may predict but would not alone preclude all positive STD screening findings. It is essential that sequential STD screening of donors continues and that genitourinary physicians should be involved in this process. Validation of newer diagnostic techniques as screening tests in this setting is required.
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Introduction

Artificial insemination with cryopreserved donor semen is an established procedure for childless couples in whom the male partner is subfertile. The British Andrology Society recommends screening potential donors for sexually transmitted infections to minimise the risk of transmission of pathogens to the mother and fetus, as pathogens may remain viable despite cryopreservation.[1–3] A previous study of 36 consecutive potential semen donors attending this clinic found a high prevalence of sexually transmissible infections.[4] Subsequently, a departmental protocol for screening donors was implemented in 1986. We aimed to audit findings of screening during a 4 year study period and, if appropriate, recommend changes to the screening protocol.

Table 1 Screening of donors

Initial interview:
Routine history—exclude those who have
(a) been/are at risk of HIV infection
(b) chronic viral hepatitis
(c) past history of genital herpes or warts
(d) had symptoms of STD within last 6 months
(e) multiple sexual partners*
Routine examination—exclude those with
(a) urethral discharge
(b) genital warts
(c) genital ulcers
Investigations—three urethral swabs for
(a) Gram stain and selective culture for *Neisseria gonorrhoeae*
(b) aerobic and anaerobic (Amies medium) culture
(c) Herpes simplex virus (virus transport medium) culture
first void urine for *Chlamydia trachomatis* (EIA, Dako)
—Serological tests for
(a) *Treponema pallidum*
(b) cytomegalovirus
(c) human immunodeficiency virus
(d) hepatitis C virus
(e) hepatitis B virus
Management and follow up:
Exclude or discontinue donors
(a) fulfilling initial exclusion criteria
(b) with viral infections
any recent seroconversion, including to CMV, is an exclusion criteria
Rescreen donors
(a) regularly (at least 6 monthly) or if change of sexual partner
(b) if clinically indicated for example, development of any genital symptoms
(c) at end of donating period
repeat tests for HIV, hepatitis B and C 6 months after last donation

*Defined, by some authors, as more than one sexual partner within the preceding 6 months[9] but unspecified in UK guidelines.[1]

Methods

POPULATION

Men referred by the Department of Obstetrics and Gynaecology to the Department of Genitourinary Medicine as suitable semen donors were screened for potentially transmissible infections. An initial assessment by the referring clinic determined potential donors and excluded those with transmissible genetic disorders, inadequate post-thaw semen quality, or who were felt to be at high risk of sexually transmissible infections.[5]

A retrospective review of all case notes of men referred for semen donor screening during the period 1 January 1992 to 31 December 1995 was undertaken. The protocol for screening potential donors is summarised in table 1.

Our current guidelines recommend the initial exclusion of donors felt to be at high risk of

Table 2 Demographics

	No of 173	*%*
Mean age (SD)	26·8 (6·1)	
Ethnicity:		
White	157	97
Afro-Caribbean	4	2·4
Asian	1	0·6
Marital status:		
single	121	75
married	36	22
divorced/separated	5	3
Occupation:		
student	79	49
employed	70	43
unemployed	13	8
Previous STDs	7	4
Sexual history		
> one partner in previous 6 months	22	13
Mean number of partners (range)		
3 months	0·77	(0–4)
6 months	1	(0–15)*
12 months	1·3	(0–20)*

*One man with multiple partners; otherwise all ranges (0–4).

transmissible infections. Those with evidence of bacterial infection, including *Chlamydia trachomatis*, may be treated and, following tests of cure and contact tracing, these individuals may then donate. Donors are required to be rescreened when they have completed donation, which usually takes 4–6 months, and also, ideally, after any partner change during the donation period. Condom usage with sexual partners is encouraged. Repeat HIV, hepatitis B, and hepatitis C antibody tests are required 6 months after the period of donation.

Results

A total of 175 men were referred for screening; two declined HIV antibody testing and were excluded. Demographic details of the 173 screened men are shown in table 2. They were predominately white and single; their median age was 26 years (range 18–44 years). One man reported 15 sexual partners in the preceding 6 months; otherwise all reported up to a maximum of four partners in the previous year. More than one partner in the preceding 6 months was reported by 13%.

POSITIVE FINDINGS AT FIRST VISIT

Positive findings at the first screen included four with herpes simplex virus cultured from the urethra; using monoclonal antibodies, two were typed as HSV-2, and two were HSV-1. Four men had non-specific urethritis (⩾ five polymorphonuclear leucocytes per high powered field on urethral smear and pyuria on two glass urine testing) and three had asymptomatic urethral carriage of group B streptococcus. Cytomegalovirus (CMV) seroprevalence rate was 26%; semen from these donors is used for CMV seropositive recipients as has been described previously.[6] Other findings included two equivocal chlamydia tests (urine enzyme immunoassay (EIA) positive, DFA test negative) which were both negative on repeat testing of early morning specimens. Similarly, two men had equivocal microscopic evidence of non-specific urethritis which was not present on early morning specimens.

During the audit period, 109 donors (63%) were re-screened following donation. The median time between visits was 255 days (range 101–635). Of those not reattending, some were excluded in the intervening period because of subsequent poor semen samples or for medical reasons (for example, one man was later diagnosed as having diabetes mellitus, another sexually acquired acute hepatitis B). The majority, however, simply failed to attend to donate; these were usually students who moved away from the area.

POSITIVE FINDINGS AT SECOND VISIT

Of those 109 who were rescreened, 13 had positive findings. Three had genital warts, of whom one also had non-specific urethritis, one had chlamydial urethritis, and three others had non-specific urethritis. Six had asymptomatic urethral carriage of *Ureaplasma urealyticum*. Other findings included one equivocal chlamydia test (urine EIA positive, DFA negative) and one with equivocal microscopic evidence of non-specific urethritis, both of which were negative on repeat testing of early morning specimens. Another man was named, during his donation period, as a previous consort by a female patient who attended with chlamydial pelvic inflammatory disease. All investigations including serological MIF titres on two occasions failed to show any evidence of chlamydial infection, past or present, and he was allowed to continue as a donor.

At the first screen, the only predictive demographic factor for positive screening findings was a history of more than one partner in the previous 6 months, with a p value of 0·005 and an odds ratio of 7·11 (table 3). Of those rescreened, no demographic factors were predictive of positive findings (table 4) and, of note, positive findings in those reporting a higher rate of partner change did not achieve statistical significance.

Table 3 Predictive factors at first screen

	Negative	*(n = 162)*	*Positive*	*(n = 11)*
Mean age	26·8		26·8	
Single (%)	121	(75%)	8	(73%)
White	157	(97%)	11	(100%)
Student	79	(49%)	6	(55%)
Past STD	6	(4%)	1	(9%)
Relationship < 3 months	10	(6%)	2	(18%)
> one partner in 6 months	17	(10·5%)	5	(45%)**

**p = 0·005 (Fisher's test); OR 7·11 (CI 1·66–30·4).

Table 4 Predictive factors at second screen

	Negative	*(n = 96)*	*Positive*	*(n = 13)*
Mean age	27·3		26·1	
Single (%)	68	(71%)	10	(77%)
White	94	(98%)	12	(92%)
Student	45	(47%)	5	(38%)
Past STD	3	(3%)	1	(8%)
New partner	29	(30%)	6	(46%)
> one partner in 6 months	8	(8%)	3	(23%)

Discussion

Screening of this preselected population found a number of asymptomatic infections despite the initial exclusion of those felt to be at risk. The initial infection rate of 6·3%, excluding CMV seropositivity, and rescreening rate of 12% are considerably lower than the rate of

33% found in the 1986 pilot study and also lower than in other studies.[4 7 8] In 1986, study participants were not preselected in that all men expressing an interest in semen donation underwent STD screening. Subsequently, a departmental protocol was implemented which initially excludes those felt to be at risk of sexually transmissible infections on the basis of sexual history.[5] In addition, efforts have been made during recent years to focus recruitment upon men who already have healthy children and are in stable sexual relationships. In this study, only 49% of donors were students, compared with 77% of the pilot group and mean age was 26·8 years (range 18–44), compared with 22·9 years (range 18–37) in 1986. In Sheffield, STD rates in men are maximal among males aged 20–24 years.

Recent partner change was a significant risk for initial positive findings but not for findings at subsequent screening. This may be due to infections with longer incubation periods such as genital warts or to other confounding factors; for example, contact tracing for two men found to have urethritis (one non-specific urethritis, one chlamydia) at rescreening revealed that their consorts had other partners. Hence screening on history alone and excluding donors reporting recent partner change would not preclude all positive findings.

Organisms transmissible in semen, including HIV, may remain viable after cryopreservation.[2 3 9] The rate of pathogen transmission to recipients of cryopreserved semen remains unclear but it is assumed to be low. There may be however under-reporting of cases; either because of uncertainty as to the specific aetiology of an infection, the initial infection may be subclinical or the link between long term complications and the insemination procedure may not be recognised.[10] There may also be a lack of awareness or unwillingness to admit that insemination is a potential source of infection. Recipients expect infection-free donor semen. Even if the risk of pathogen transmission to recipients is currently low, our aim should be to maximise safety and ensure that the risk is negligible. There is no absolute method of ensuring that infectious agents will not be transmitted by donor semen but screening in accordance with the most up to date recommendations should make it a more remote possibility. Some of the currently available screening tests are not ideal, however, and deciding which are optimal for screening is problematic.

Detection of *Chlamydia trachomatis* is more sensitive from urethral rather than semen samples using cell culture or enzyme immunoassay.[2] Enzyme immunoassay of first void urine is a less invasive alternative to urethral swabs although overall sensitivity may be lower in asymptomatic men than in those with urethritis.[11] Newer diagnostic techniques such as polymerase chain reaction or ligase chain reaction appear more sensitive than other methods, including culture, for detection of *Chlamydia trachomatis* either in semen[12] or in urethral and urine samples.[13 14] As yet, there has been no direct comparison of these different specimen sources and the optimal specimen type is still unclear.

Detection of asymptomatic urethral shedding of herpes simplex virus (HSV) using urethral viral culture is limited by the frequency of sampling as viral shedding may be intermittent. Semen viral cultures are usually negative because of the cytotoxicity of semen[10] and reliable type specific serological testing is as yet only a research tool in this country. A recent seroepidemiological UK survey found 17·3% male GUM clinic attendees and 3·2% male blood donors to have HSV type 2 antibodies.[15] Overall, 45% of participants with HSV type 2 antibody reported symptoms suggestive of genital herpes and only 27·4% had had genital herpes diagnosed, emphasising that most of those infected have no symptoms or are unaware of their infection and therefore could not be excluded from semen donation on history alone. When type specific testing becomes commercially available, it will be feasible to exclude seropositive donors. Should this be limited to only those who are HSV-2 seropositive? A high proportion of type 1 isolates in genital herpes among GUM attendees has been reported[16 17] and Cowan *et al* report 16·5% of their study participants with a history of genital herpes had antibodies to type 1 alone.[15] With HSV-1 seroprevalence rates in London of 55% GUM clinic attendees and 44% blood donors (F Cowan, personal communication), exclusion of all HSV-1 seropositive donors would have obvious implications for donor recruitment. One suggestion is to exclude HSV-2 positive donors initially with subsequent exclusion of any donors undergoing seroconversion to HSV-1 or HSV-2 during follow up.[18] Another alternative would be to use semen from HSV-1 positive donors only for HSV-1 positive recipients but the possibility of transmission of different strains can not be ruled out.[19] Further research is required to determine the value of type specific serological testing as a screening tool in this setting.

Screening guidelines recommend the exclusion of men with genital warts[1] as human papillomavirus (HPV) infection may be a marker of other sexually acquired infections and because of its association, particularly types 16 and 18, with female genital malignancy. Using polymerase chain reaction, semen HPV DNA have been detected in males with and without genital warts,[20] 100% of those with intrameatal warts, 56% with non-intrameatal penile warts, and 41% of those without warts were HPV DNA positive. It has not yet been determined, however, whether small quantities of detectable viral DNA represent infectious virus. Even if reliable DNA tests were routinely available, it is unclear whether asymptomatic carriers of HPV, detected by such methods, should be excluded from semen donation.

Ureaplasma urealyticum is a frequent commensal of the genital tract but may be an important opportunistic pathogen during pregnancy; ureaplasmal chorioamnionitis is associated with prematurity and it may also

cause neonatal septicaemia, meningitis, and pneumonia.[21] Screening for *Ureaplasma urealyticum* in donors is currently recommended but is not mandatory. In our study, urethral cultures for *Ureaplasma* were all negative initially with 6/109 (5·5%) positive at rescreening. This finding is considerably lower than in other studies[7 8] and may reflect differences in our population. Four men who were positive only at rescreening denied new partners and the possibility of initial false negatives can not be ruled out. Detection of *Ureaplasma urealyticum* using PCR has greater sensitivity and a shorter time requirement than culture[22] but this is not yet routinely available. Two men who were *Ureaplasma* positive reported several partner changes during the donation period; as this may have been new infection, they were excluded. There is no consensus on the management of *Ureaplasma* in semen donors and more information is required to clarify the current situation. STD screening needs to be acceptable to donors and remain cost effective. The use of techniques, such as PCR and LCR, to detect a wide range of pathogens in semen, urine, and serum would provide rapid sensitive screening tests and would obviate the need for more invasive methods. Until these newer methods are validated in routine clinical practice, and become less expensive, our screening protocol is unlikely to change. Currently, screening costs can be minimised by excluding high risk donors, on the basis of medical and sexual history details, and ensuring adequate post-thaw semen quality before STD screening as most donors are excluded on the basis of semen quality rather than STDs.[23]

Less than 20% of initial volunteers will fulfil the full criteria of high quality post-thaw semen, no transmissible genetic disorders, and no transmissible pathogens. Deciding to exclude all those with recent partner change may further reduce positive findings but would not preclude them and would also make it more difficult to achieve adequate donor numbers. It is, therefore, essential that sequential STD screening of donors continues and that genitourinary physicians should be involved in this process. Validation of newer diagnostic techniques as screening tests in this setting is required.

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